Introduction to Neuroscience & Neuro-Instrumentation
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Lecture No. 14
Introductory Neuroscience & Neuro-Instrumentation:
Axonology, Neuronal Biophysics (2)

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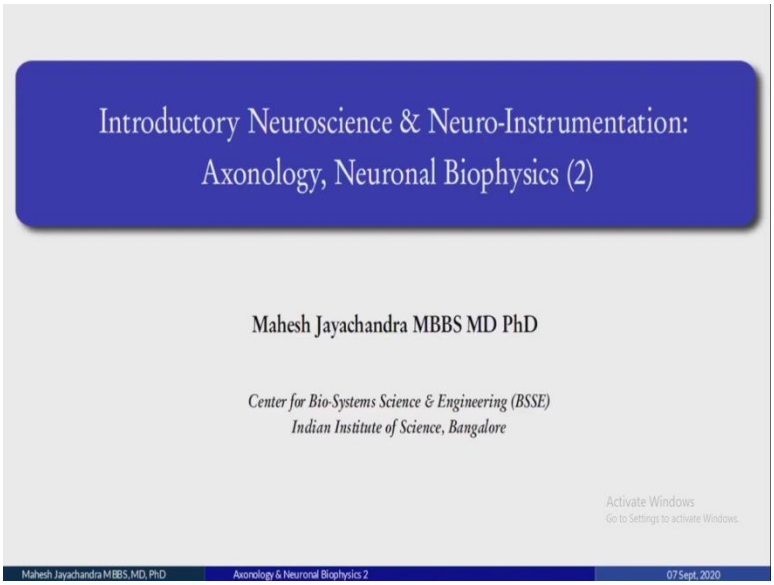

So, introductory neuroscience and neuro-instrumentation: axonology and neuronal biophysics, part two.

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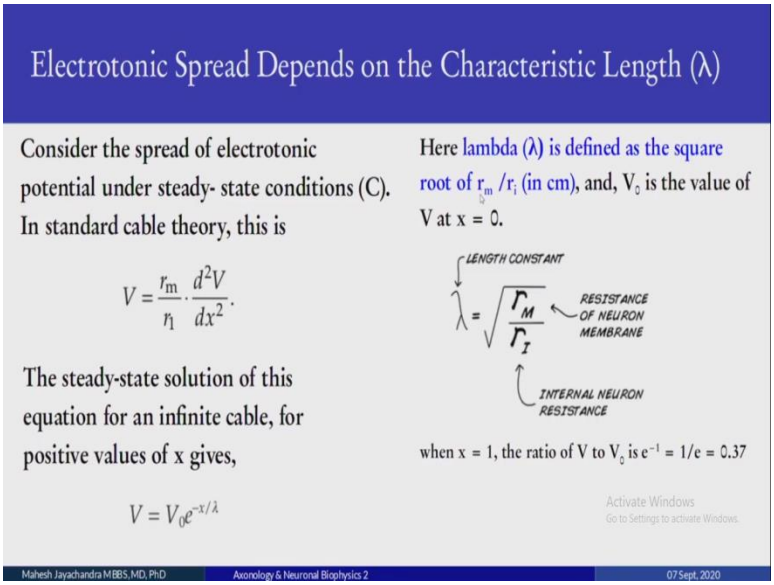

So, we were talking about the passive spread or electrotonic spread of potentials across dendrites, across axons. And this depends on something called the characteristic length or Lambda. So, consider the spread of electrotonic potential under steady-state conditions. In standard cable theory, this equation defines it where V is voltage, then you have the, a term for membrane resistance, you have a term for internal resistance and this is d square v by dx square is its spread over the length of the axon, the spread of the voltage length of the axon.

So, the steady-state solution for this equation in an infinite cable for positive values of x gives

$V = V_0 e^{-x/\lambda}$

And here, this is very straight forward to derive from cable theory. And here, this term Lambda is defined, it is defined as the $\sqrt{r_m/r_i}$. So, the resistance of the membrane, neuronal membrane, is divided by the internal resistance of the neuron. And V_0 is the value of v at X=0. So, when x = 1, the ratio of V to $V_0 e^{-1/\lambda}$ or 1/e or 0.37. So, it reaches 0.37 of its original value, where x=1.

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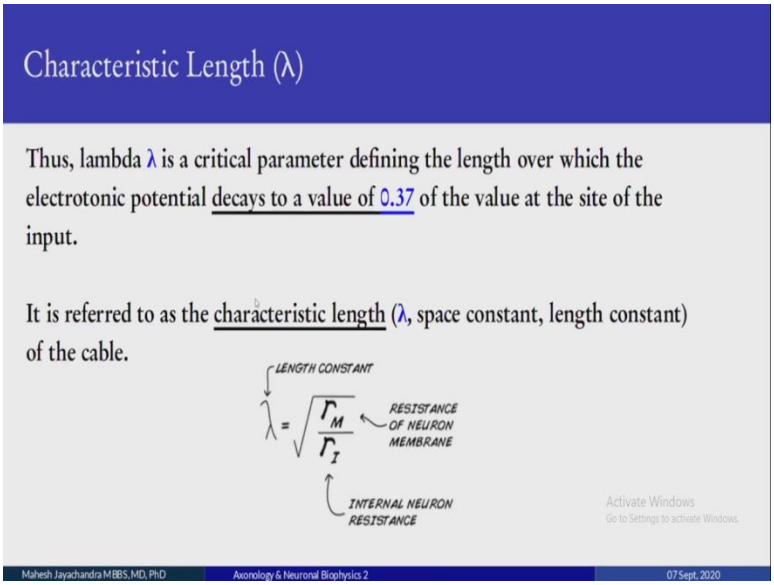

So, therefore, Lambda is a critical parameter defining the length over which the electrotonic potential decays through a value of 0.37 from the original value at the site of input. So, this is referred to as lambda, it is also referred to as characteristic length, it is referred to as space length or it is referred to as the length constant of the cable.

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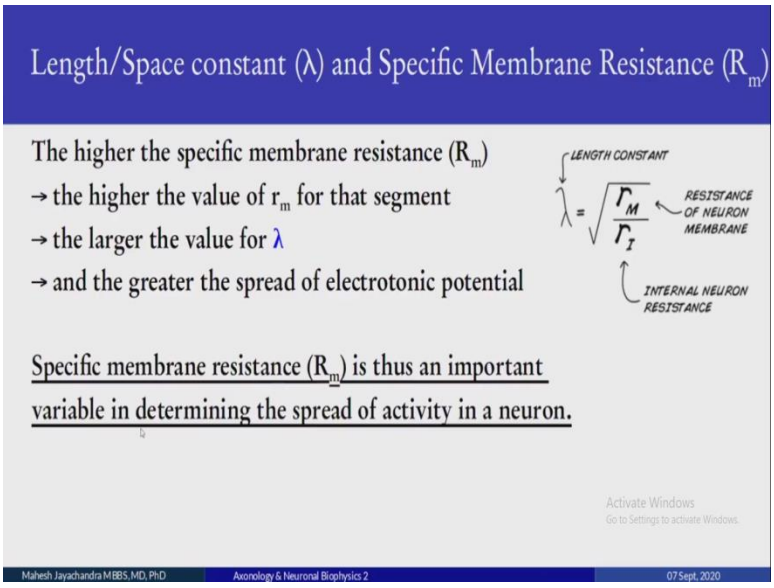

So, the higher the specific membrane resistance, capital R_m leads to a higher value of r_m for the segment, which is the resistance of a patch of membrane. So, therefore the value of Lambda is bigger and so the electrotonic spread, potential spreads more. So thus, specific membrane

resistance capital R_m is an important variable in determining the spread of activity, this passage electrical activity in a neuron.

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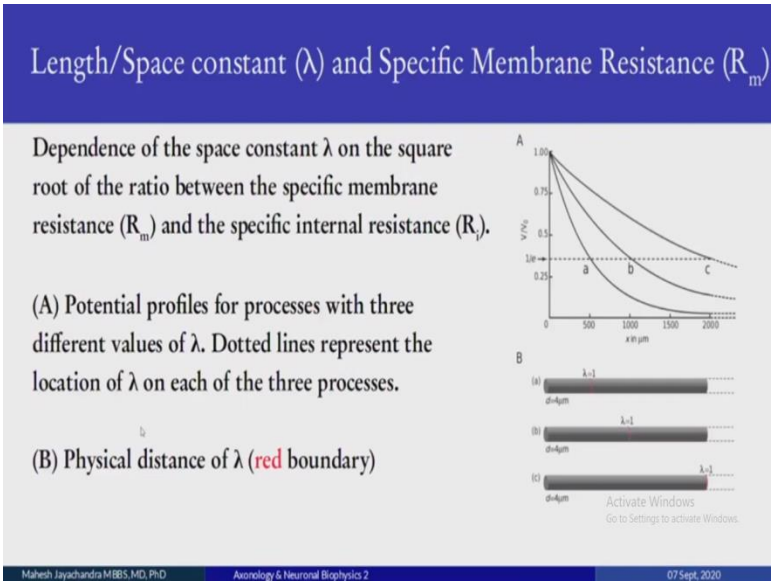

So, length and space constant and membrane resistance. So consider, you know, an axon, 3 axons with 3 different values of lambda, this is Lambda of the first, this curve, this is the second, this curve and this is the third, this curve. So, the potential profiles for all these different values are on top over here and the dotted lines represent the location of lambda on each of these processes, the physical distance is shown in red. So in the first case, because of the properties, it is only so much, in the second case it is much more and in the third case, it is even more.

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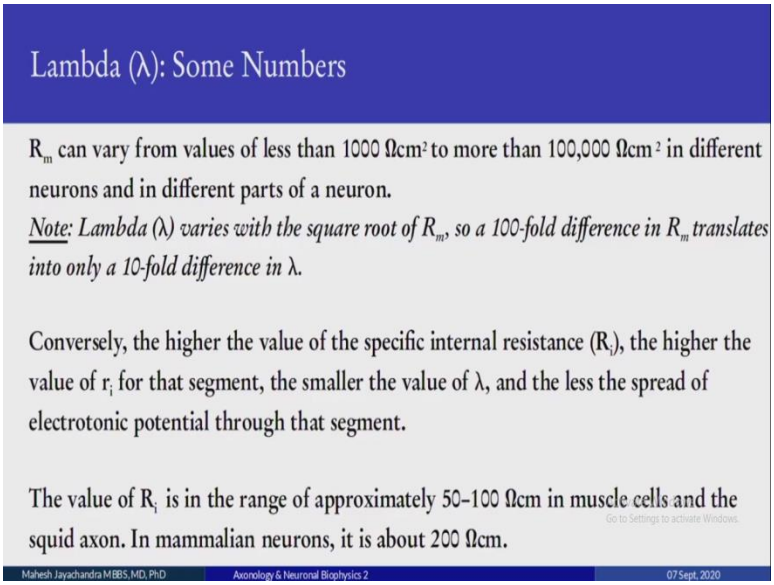

So R_m, some numbers R_m can vary in values from less than 1 k ohm centimeter square to more than a 100 thousand ohm square centimeter in different neurons and different parts of a neuron. So note, that lambda varies with the $\sqrt{R_m}$. So, a 100 fold difference in R_m translates to only a tenfold difference in lambda. Conversely, a higher value of specific internal resistance R_i, so the higher the internal resistance, r_i, for that segment the smaller the lambda and the less the spread of the potential through the segment.

Because the resistance prevents the electric current from spreading. So, the value of R_i is approximately in the range of 50 to 100-ohm centimeter muscle cells and squid axon. In mammalian axons, you know, in mammalian neurons, it is much higher, about 200-ohm centimeter.

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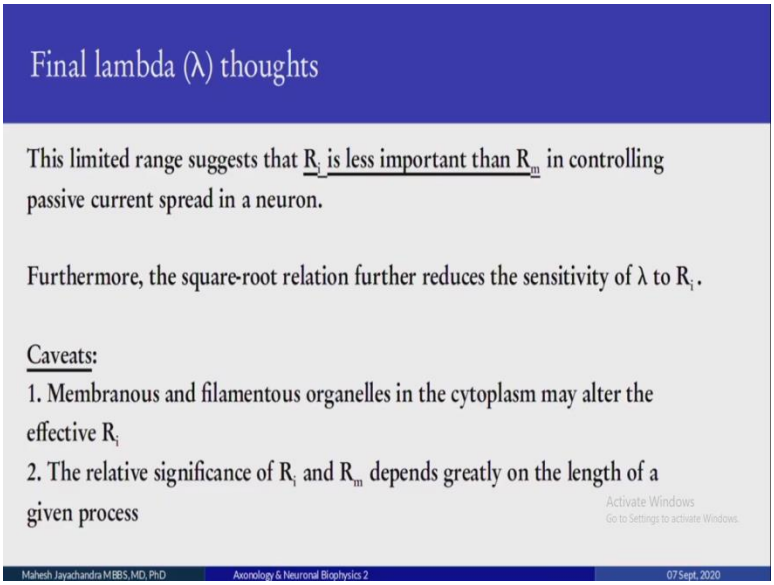

So, this kind of limited range suggests that R_i is less important than R_m in controlling the passive of current spread in the neuron i the internal resistance of an axon is not so important as the membrane resistance of the axon, as far as the passive spread of electronic spread of electrical activity in the neuron. Furthermore, it is a square root relationship. So, it further reduces the sensitivity of lambda to R_i. However, there are some caveats.

So, in the cytoplasm, you have membranous and filamentous organelles, tubules, various things mitochondria, endoplasmic reticulum, which we looked at in the microscopic anatomy of the central nervous system. All these may change the effective R_i and also the relative significance of R_i and R_m depends on the length of the given processes and how branched it is and so forth.

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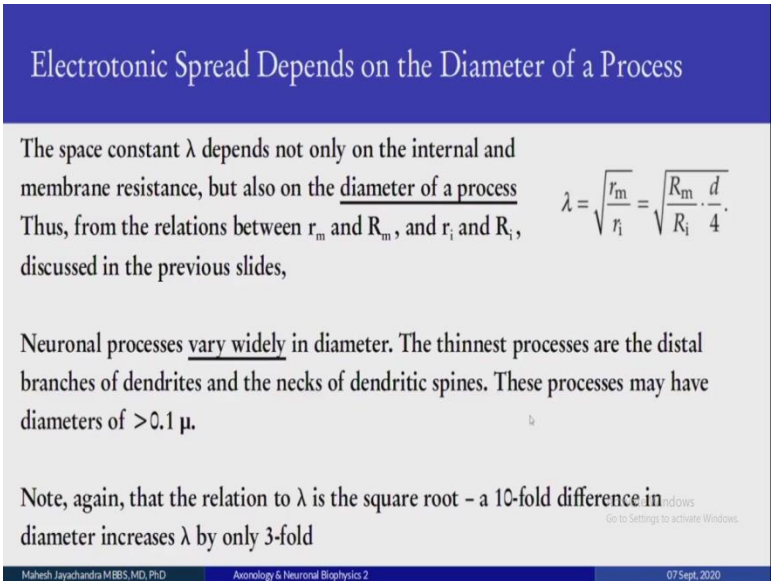

So, the space constant also depends on the diameter of the process besides the resistance which we considered before. So, thus from the relationships of r_m and R_m, r_i and R_i, discussed in the previous slides you can,

$\lambda = R_m / R_i$

and that reduces to the square root of the specific membrane resistance, specific internal resistance, and the d/4 is the, a term for the cross-sectional area.

So, neuronal processes vary very widely in diameter. The thinnest processes are the distal branches of dendrites and the necks of dendritic spines. These have diameters of greater or equal to 0.1 mu. Note again, that the relationship of Lambda is to the square root. So, a tenfold difference in diameter increases lambda by only 3 times.

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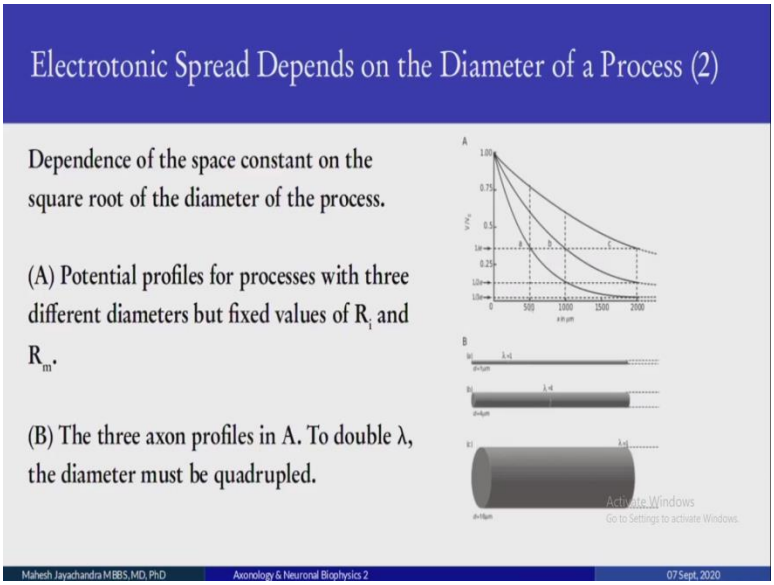

So here, we have the relationship of lambda to diameter. So again, you have 3 different axons with 3 different diameters 1 mu, 4 mu, and 16 mu. And you see the potential profile, so lambda in the first one is over here, in the second one is here and the third one is here because you know, it spreads much further because its cross-sectional area is much more. So the 3, to double lambda, the diameter must be quadrupled.

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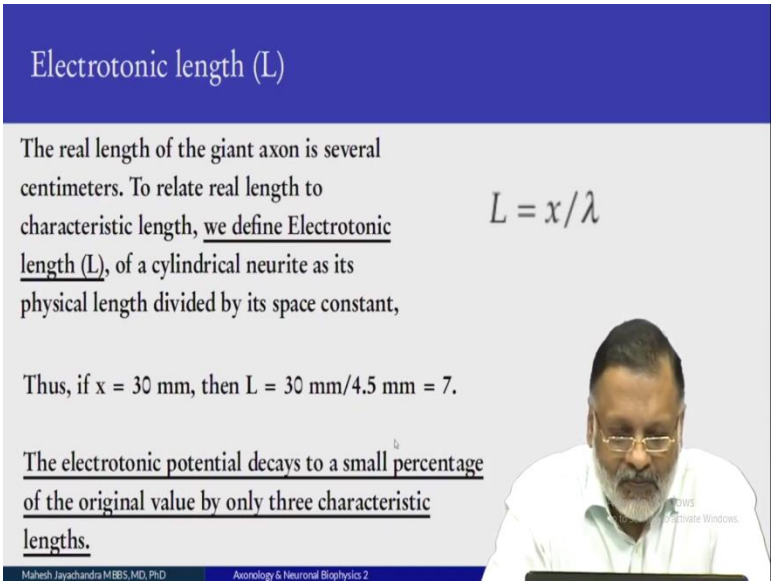

So, the real length of a giant axon is several centimeters. So, to relate this real length to the characteristic length or lambda, we define electrotonic length or L of a cylindrical neurite as its

physical length divided by its space constant. So thus, if x is 30 millimeters, then L would be, that is the electrotonic length 30/4.5 = 7. So, the electrotonic potential decays to a small percentage of the original value by 3 characteristic lengths. So, this has implications when stimulating a nerve.

So, you can stimulate a nerve and for whatever reason, experimental conditions, you know, it goes down, it can move by 3 characteristic lengths and then you have a brand new zone to stimulate and the previous area does not affect the new stimulatory site.

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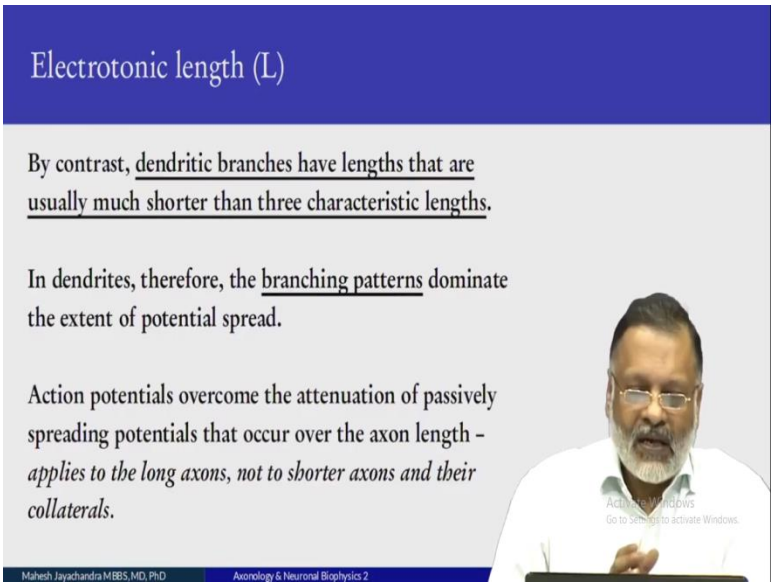

But these were axons that we discussed so far. If you look at dendrites, they have lengths that are very much shorter in size than axonal lengths and characteristic lengths. So, therefore in dendrites, what is important is the branching patterns, you know, which modulate the extent of potential spread. So, action potentials overcome the attenuation of passively spreading potentials that occur over axon length. But this occurs to long axons, not too short axons and their collateral.

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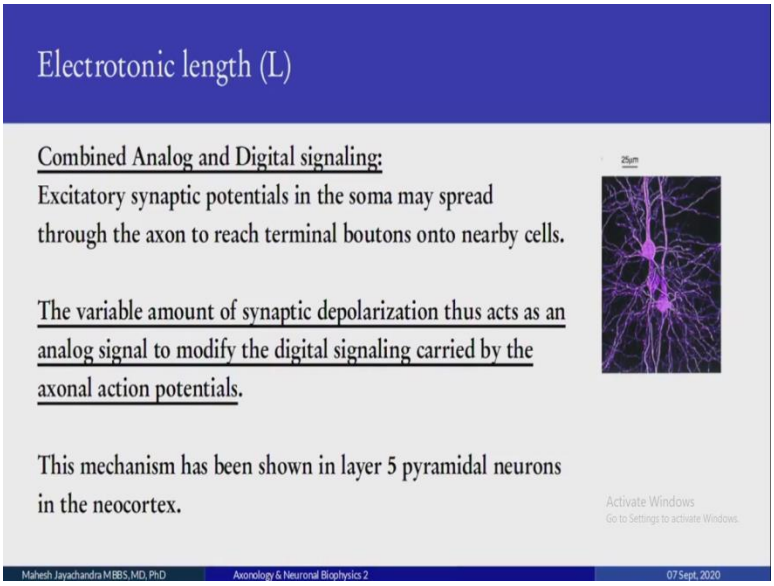

So, putting all this together, we have combined analog and digital signaling in neurons. So, you have the pyramidal cells over here on the right, couple of them, and you have their extensive dendritic branches and you would have from the base, these cells axons leading onto other cells- one over here, one over here and there is one behind actually 3 of them over there. So, you have excitatory synaptic sites on the soma and they get inputs from different cells, different networks, and, depending on the amount of excitation, the amount of inhibition, they modify the analog signals.

The analog signals reach a threshold. Once it reaches a threshold, you have action potentials that are kind of digital, all or nothing, and coded by frequency. So, these mechanisms are seen in, have been found in pyramidal cells. So again, so you, think of analog computer over here, analog computation occurring in the dendritic branches and this modulates action potentials coming out from the digital neurons. So, a single cell is a combined analog and a digital supercomputer.

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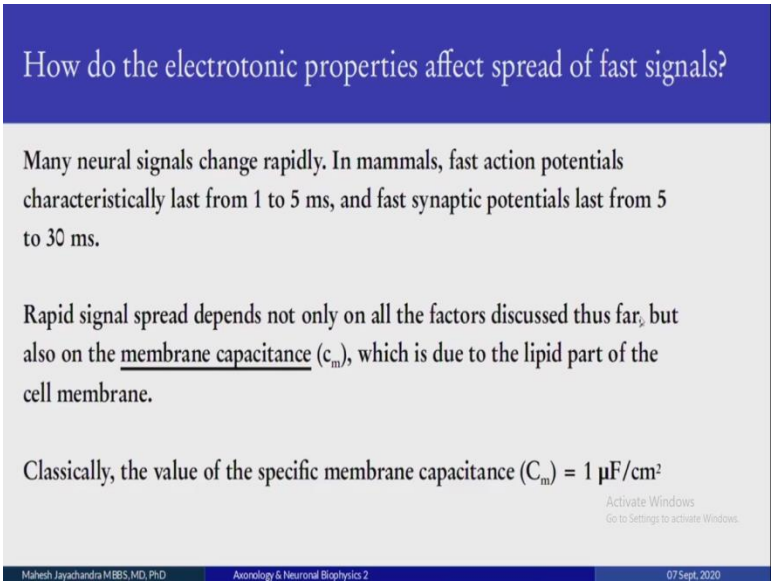

So fast signals, so how do electrotonic properties affect the spread of fast signals? So, many neural signals change rapidly. So, in mammals, you have fast action potentials that last from 1 to 5 milliseconds. And fast synaptic potentials that last from 5 to 30 milliseconds. So, rapid signal spread depends not only on all these factors discussed so far but also on the membrane capacitance because when there is a rapid change, capacitative effects come into play.

And of course, to remind you, the capacitance is due to the lipid part or the lipid moiety of the cell membrane. And classically, we put the value of specific membrane capacitance, C_m as 1 microfarad per centimeter square.

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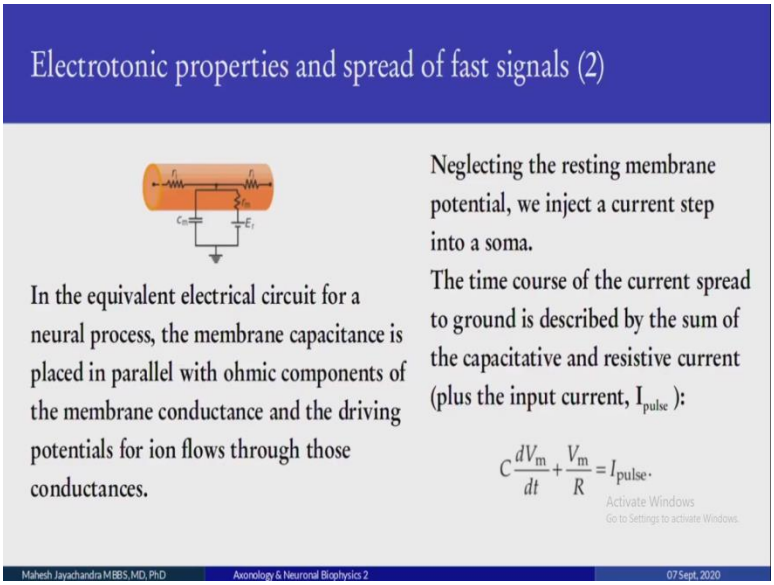

So, continuing with electrotonic properties and the spread of fast signals. So, here you have the equivalent circuit of the renewal process. The membrane capacitance is in parallel with the ohmic components of the membrane conductance the electromotive force and the driving potential. And neglecting the resting membrane potential, what we do is, we inject current into a cell body. So, the time course of the spread of current is described by two currents one is the capacitative current, the part which discharges and recharges the membrane, and the resistive current plus of course the input current which you give during the pulse.

So, this would describe it, the capacitance. Then you have a resting membrane potential that changes. Then you have a membrane potential and then you have the resistance and that is equal to the current pulse.

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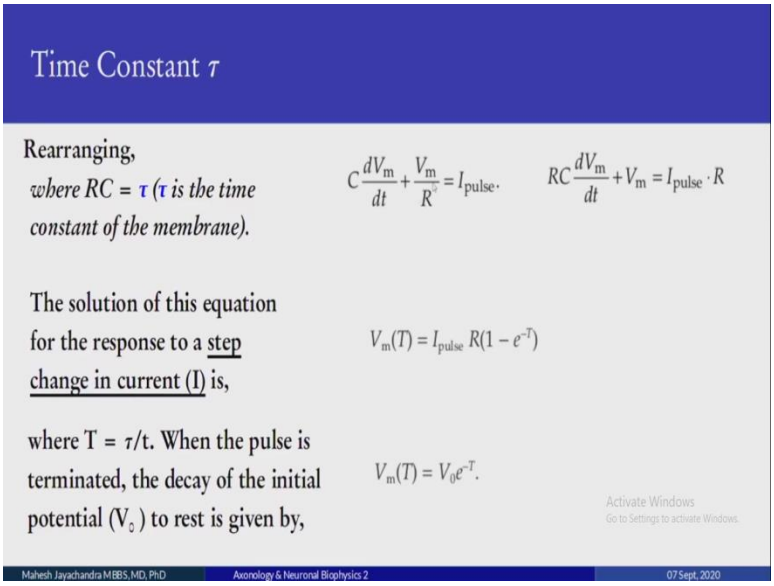

So if we rearrange this, and we substitute RC = τ which is the time constant of the membrane, we get this by rearranging, we get this. And the solution for this equation for a response to a step current change in potential is given by this equation where T = τ/t. When the pulse is terminated, the decay of the initial potential to rest is given by this equation. So, it comes back to baseline and again you see e and e^{-t}.

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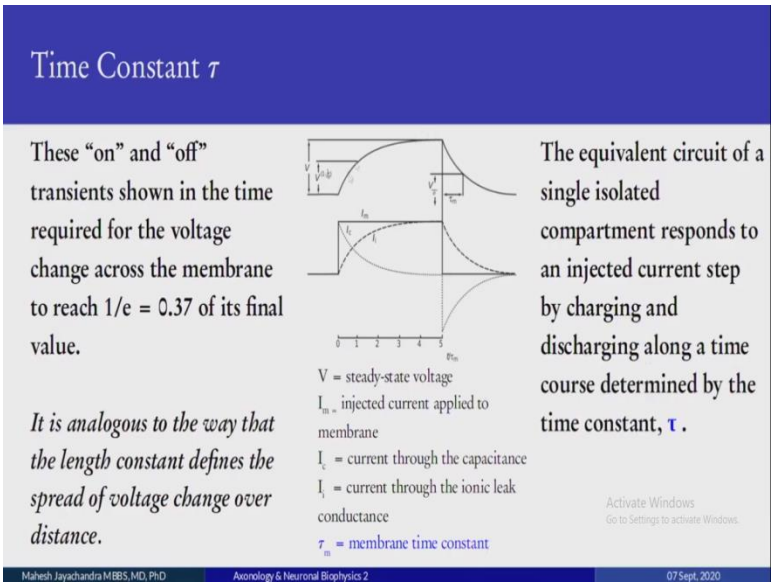

So, what happens? So you have and "on" transient and then you have an "off" transient. This is how it looks. You have a step current coming in here and it takes some time for the membrane capacitance to discharge, recharge, to reach that thing. And when you switch it off, this is a square pulse. It again decays back to normal. So, the on and off transient shown in the time required for the voltage change across the membrane to reach 1/e of its final value which is 0.37 So, this is similar to the way the length constant defines the spread of voltage over distance.

So, the equivalent circuit of a single isolated compartment responds to an injected step current by charging and discharging along a time course determined by the time constant tau. And we, for this figure, V is a steady-state voltage. I_m is the injected current applied to the membrane, just an electrical square pulse on top of the axon. I_c is a current through the capacitance. I_i is the current through the ionic leak conductance. And τ is the membrane time constant.

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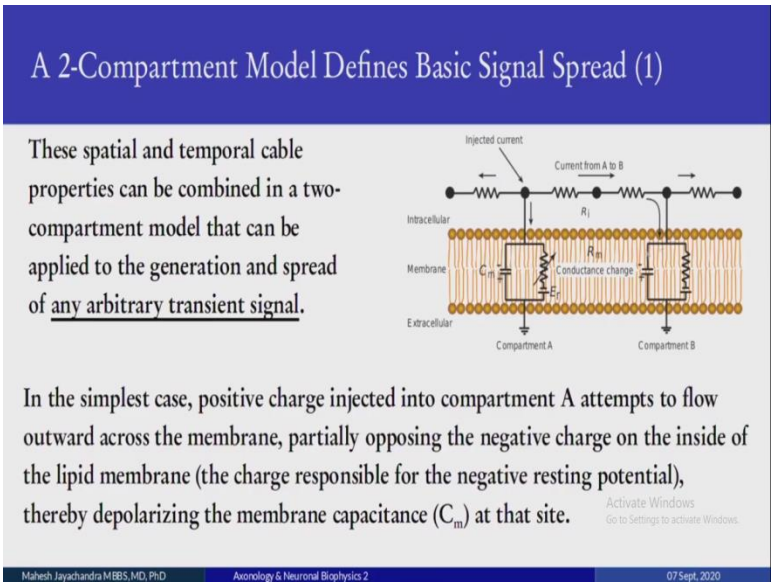

So, consider a two-compartment model. So you have two compartments, there is one compartment here and there is one compartment here. This is compartment A and this compartment B. So in compartment A, you have its equivalent circuit, you have the capacitative term and you have the resistive and the EMF term. Likewise, with B. So, this very simple two-compartment model can be applied to the generation spread of any arbitrary transient signal.

So, consider the simplest case. So, this is compartment A and you inject current, positive charge here. And this flows outward across the membrane, partially opposing the negative charge on the

inside of the lipid membrane. This negative charge is responsive to the resting membrane potential. And thereby, it depolarizes the membrane capacitance at this site.

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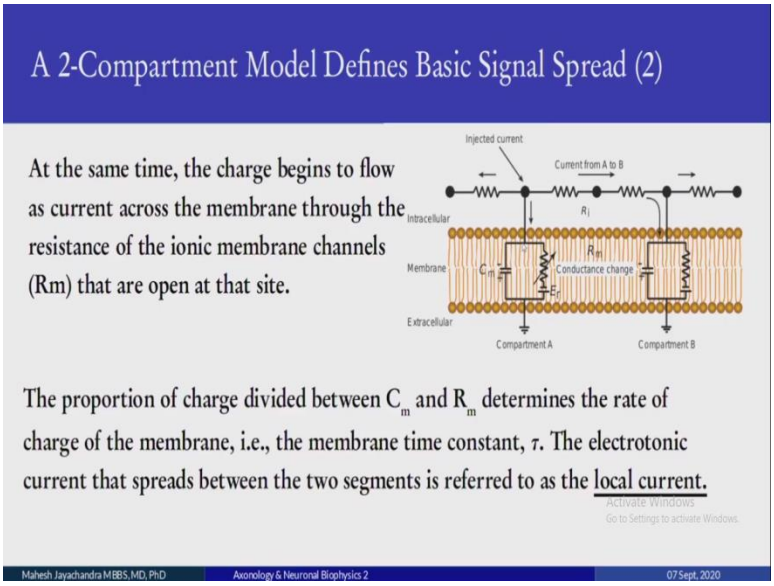

At the same time, the charge begins to flow as a current across the membrane through the resistance of the ionic membrane channels that are open in this site, across the membrane. And the proportion of charge divided between C_m and R_i determines the rate of charge of the membrane, which is the membrane constant. So, the electrotonic current which spreads from one compartment to another is also called the local current.

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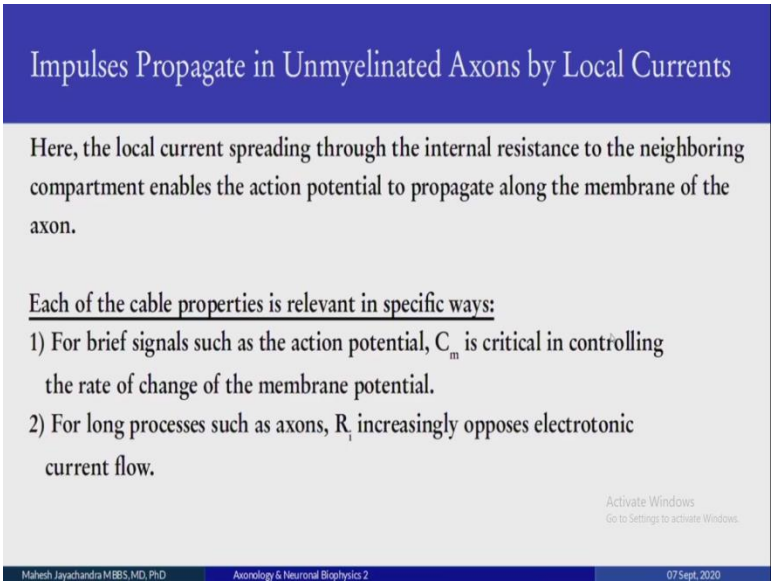

So, in unmyelinated axons, if you remember, some axons have myelin insulating them, some of them are unmyelinated. In an unmyelinated axon, the local current spreading through the internal resistance allows the propagation to the next compartment. So, each of these cable properties is relevant in specific ways. So, for brief signals such as an action potential, C_m the capacitance is critical in controlling the rate of change of membrane potential. For long processes such as axon, the internal resistance is important because it opposes the electrotonic current flow.

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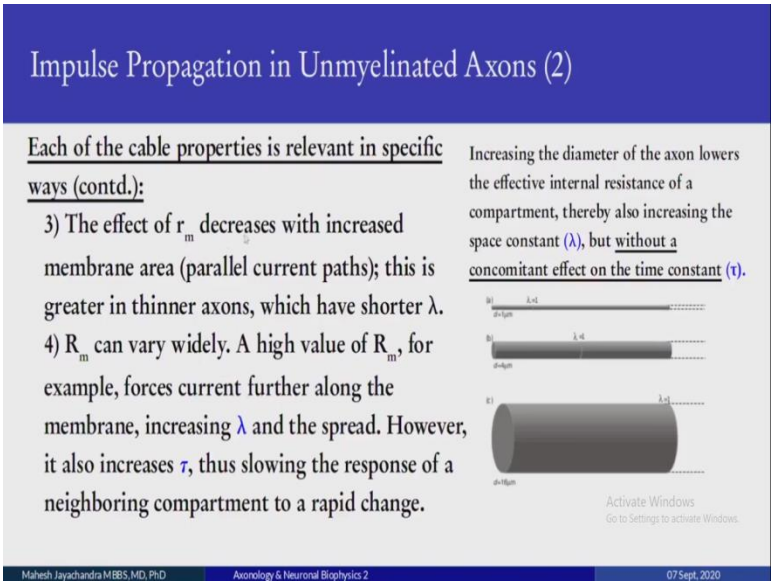

So continuing, the effect of r_m, you know, membrane resistance, decreases with increased membrane areas because of parallel current paths. This is greater in thinner axons that have a shorter lambda. Specific resistance, R_m, can vary widely. So if it is high, then the current is forced to spread along the membrane, increasing lambda and spread. However, at the same time, tau is also increased, because if you remember, $\tau = RC$. Thus slowing the response of the neighboring compartment to this change.

So, consider what happens when you increase the diameter of an axon, it lowers, so here it is 1 mu, 4 mu, and 16 mu. So, it lowers the effective internal resistance, thereby it increases the space constant lambda but without an effect on the time constant tau. So, these are the effects, cable properties are very important, they have very distinct effects on a local current and electrotonic spread of current in the dendritic trees.

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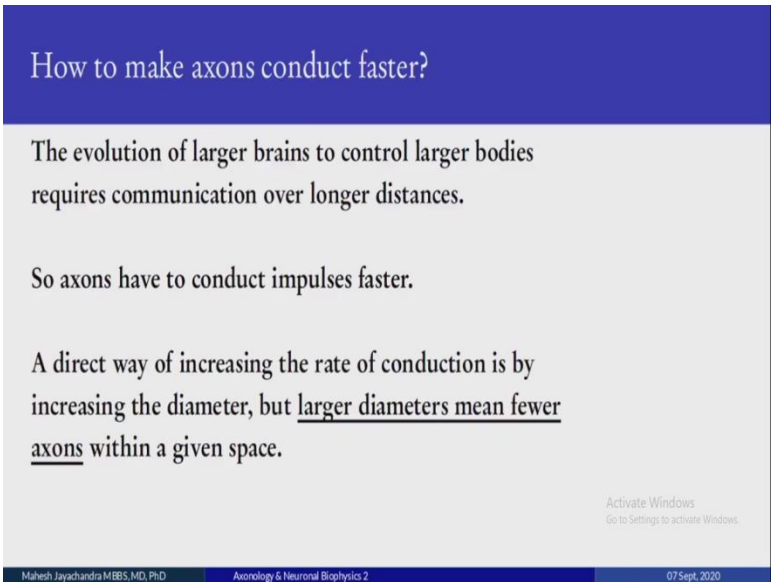

So, the question is how do you make it conduct faster? Because once you have large brains, I mean large brains compared to you know, invertebrates. So, we need to control large bodies and that requires communications over long distances. Even though it feels very fast for us, thought and stuff, the maximum speeds of axonal conduction are only about 100 to 120 meters per second in humans. And much much slower in lower forms. So, there is this problem in evolution how do you make axons conduct faster?

So one way to increase, you know, axonal conduction is to increase the diameter. But there is a limit, you know, you cannot have, the squid giant axon is probably the axon which we know with the maximum diameter. You cannot increase axon's diameters indefinitely because larger diameters mean fewer axons within a given space and fewer axons mean less cognitive processing.

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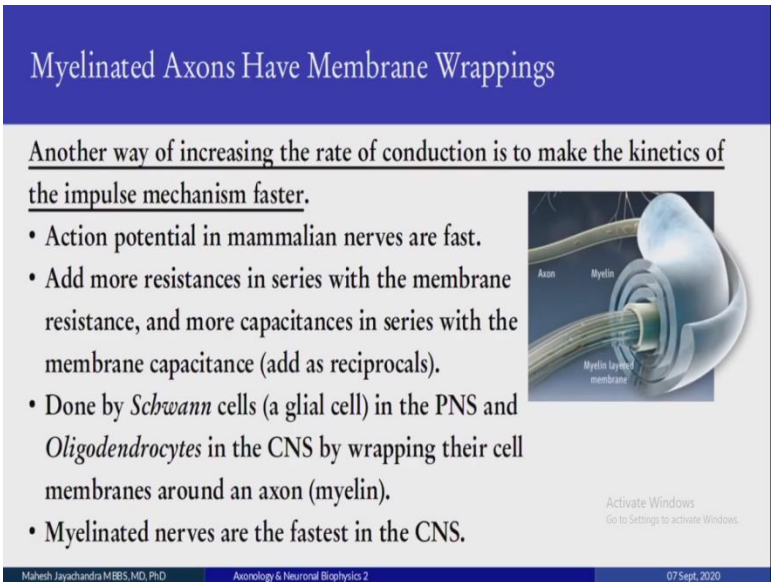

So, coming back to myelin. So one way is to increase the rate of conduction, which is to make the kinetics of the impulse mechanism faster. So, if you remember, we talked about myelin, so now we will talk about biophysics. So, an action potential in the membrane, mammalian nerves are very fast. So, with the wrapping of these cell membranes from the oligodendrocytes and the Schwann cells, more resistances are added in the series of the membrane resistances. More capacitances are in series of the membrane capacitance, remember capacitance is added as reciprocals.

And this kind of insulates and forces, you know, faster conduction. We will get to it in just a bit. So, just to remind you, these myelin layers are provided by the Schwann cells in the peripheral nervous system and the oligodendrocytes in the central nervous system, they wrap their cell membranes on an axon. And because of this, they are the fastest, myelinated axons are fastest in the central nervous system.

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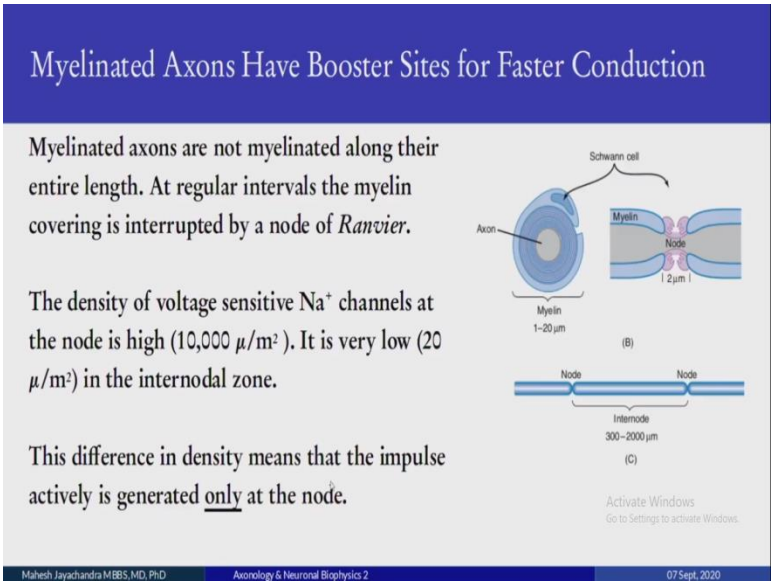

So, myelinated axons are not myelinated across the entire length. If you remember, we have nodes, nodes of Ranvier, they interrupted. So here you have a cross-section of an axon with the myelin layers and the Schwann cell over there. And here, you have the longitudinal section and here you see the node in between. So, the density of sodium channels in the node is very high, you know, about 10,000. It is much lower in the internodal regions. An internode is approximately 300 mu to 2000 mu. This difference in density means that most of the action, potential action happens at the nodes, not so much in the internodes.

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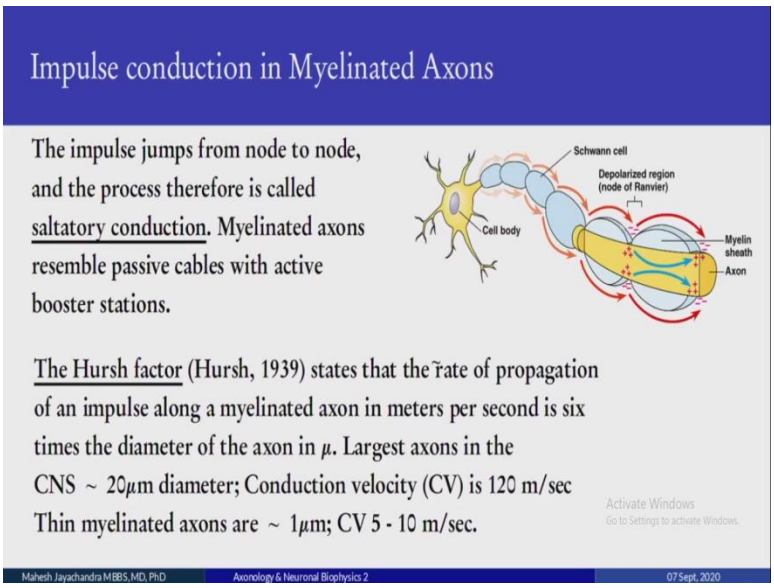

So, the impulse jumps from one node to another. And it is called saltatory conduction or leaping conduction. So, this makes it much faster. And myelinated axons, one way to think of it, resemble passive cables with active booster stations. And Hursh, in 1939, found an empirical law, that states that the rate of propagation of an impulse along a myelinated axon per second is 6 times the diameter of the axon in mu.

So, the largest neuron in the central nervous system are approximately 20 mu in diameter and their conduction velocity is 120 meters per second. Thinly myelinated axons are approximately 1 mu in diameter and their conduction velocity is only 5 to 10 meters per second. So, meters per second, very very slow compared to the transmission of electricity or light, very very slow.

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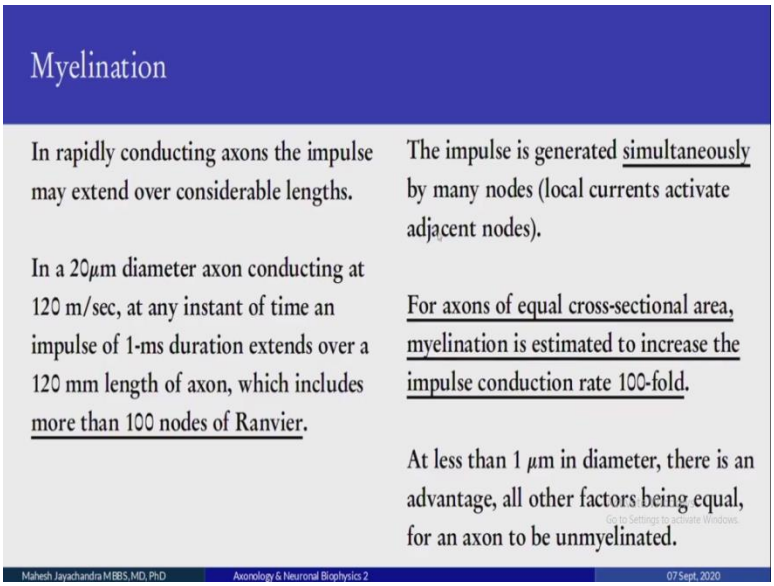

So, some more thoughts about myelination. So, because of the saltatory conduction, the impulse, the length of the impulse, it may extend over a considerable length across the axon. So, for example, in a 20 mu diameter axon conducting at 120 meters a second at any given time, an impulse of 1 millisecond, this is a typical action potential. It extends over a 120-millimeter length of axon which includes more than 100 nodes of Ranvier.

So, on action potential, even though it comes up like this and goes down, it extends over 100 nodes of Ranvier. So, this impulse is generated simultaneously by many nodes. The local currents activate adjacent nodes. So, for axons of equal cross-sectional area, they have

myelination, impulse conduction increases 100 fold. However, if the axon is less than 1 mu in diameter, and all other factors are equal, there is an advantage for the axon to be unmyelinated.

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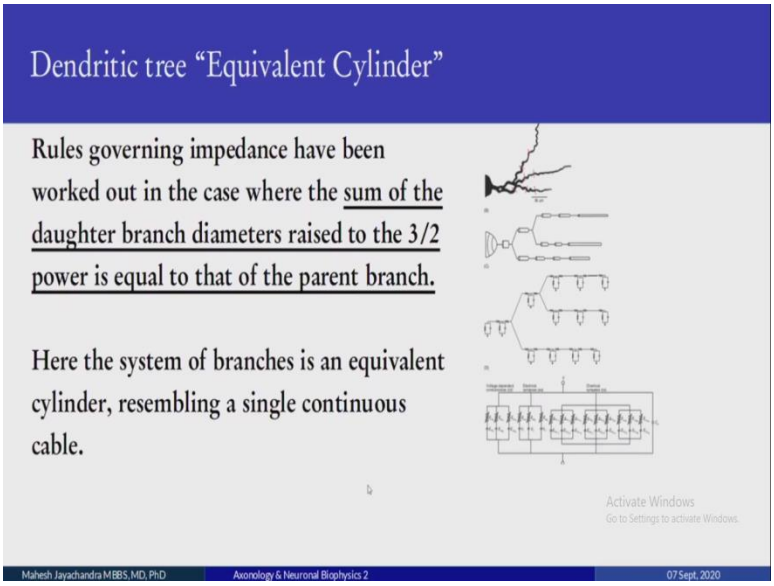

So, with all these facts, how does current spread in a dendritic tree? So, the dendritic tree constitutes a conductance load on activity and these are the different kinds of the dendritic tree, what have it is literally like the different trees in a forest. So, the spread of activity from one side is determined by the impedance match or mismatch between that site and neighboring sites. This is electrical theory.

Consider your speakers, your speakers have a particular impedance. If you use the wrong impedance, the output will be, you know, distorted or less. So, this on the below is a compartment model of a Purkinje cell in the cerebellum, I think by (23:00) group. And the soma is just a round sphere, we are not interested in the soma. The action is over here, in the dendritic branches and if you would notice, they have different diameters. And as you go to the periphery, they become thinner and thinner. And all this is electrical compartment modeling. This is not real, this is a model. But you can see how detailed it can get.

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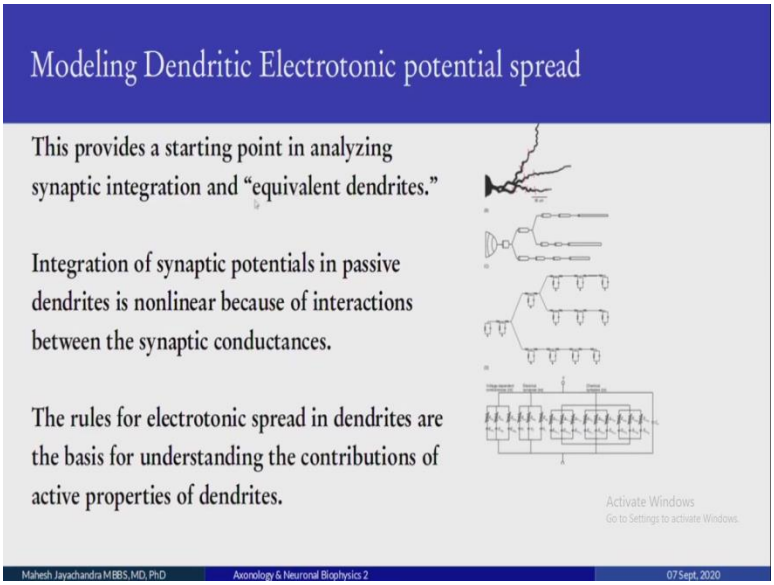

So, you have to have, get this concept of this equivalent cylinder. So again, all this stems from the work of Wilfrid Rall and (23:36), more recently. So, rules governing impedance have been worked out on a particular case, whether the sum of the daughter branches raised to 3/2, so 1.5 power, is equal to that of the parent branch. So here, the systems of branches is an equivalent cylinder resembling a single continuous cable. So, this is the actual cell, we are making it into compartments, you are putting, you know, assigning various c and r terms to each compartment and finally, you get an equivalent cylinder resembling a single continuous cable.

So when you have, such a model, it is a starting point in analyzing both synaptic integration and equivalent dendrites. So, integration of synaptic potentials in passive dendrites is non-linear because different synaptic, synapses are conductances, so they interact. So, the rules for understanding the electronic spread and electrotonic spread in dendrites are the basis for understanding the contribution of active properties of dendrites.

So, one thing to be borne in mind is that dendrites also have active conductances, so that adds another layer of complexity when you are modeling. And if you want to do realistic modeling, you have to assign and put in all these terms, whatever we get from experimental physiology has to be added. And then only, your model will replicate or kind of replicate what is happening in the real situation.

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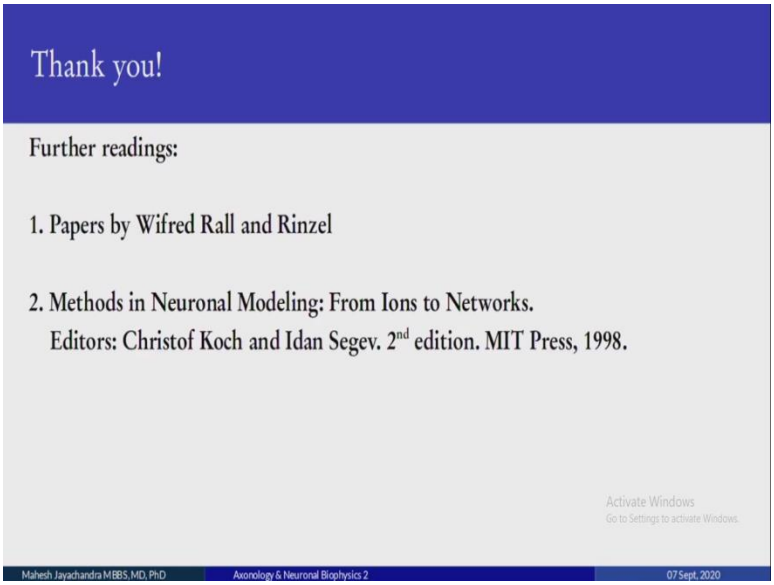

So thank you, and further readings, I strongly, if you are interested in this stuff, I recommend you to checkout Wilfrid Rall and Rinzel - Rall and Rinzel, other like Hodgkin and Rall and Rizel for cable theory. Go on PubMed, put in Wilfrid Rall and you will get a lot of his original papers. And those of you who like books, I strongly recommend Methods in Neuronal Modeling: From Ions to Networks by Christof Koch and Idan Segev. So, this is available from MIT Press and I think you have copies of it available on the internet.

So, thank you very much, this has been a slightly complex session and, but you need to know all this to realistically model neurons and that is possible. Thank you.